Female infertility

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ABSTRACT

INTRODUCTION: About 17% of couples in industrialised countries seek help for infertility, which may be caused by ovulatory failure, tubal damage or endometriosis, or a low sperm count. In resource-rich countries, 80–90% of couples attempting to conceive are successful after 1 year and 95% after 2 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for infertility caused by ovulation disorders? What are the effects of treatments for tubal infertility? What are the effects of treatments for infertility associated with endometriosis? We searched: Medline, Embase, The Cochrane Library and other important databases up to April 2004 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 56 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: clomifene; cyclofenil; drug-induced ovarian suppression; gonadotrophin priming of oocytes before in vitro maturation; gonadotrophins; gonadotrophin-releasing hormone agonists plus gonadotrophins; gonadotrophin-releasing hormone antagonists; in vitro fertilisation; intrauterine insemination plus controlled ovarian stimulation; intrauterine insemination plus gonadotrophins; laparoscopic ablation of endometrial deposits; laparoscopic ovarian drilling; metformin; ovarian wedge biopsy; pulsatile gonadotrophin-releasing hormone; selective salpingography plus tubal catheterisation; tamoxifen; tubal flushing with oil-soluble media or with water-soluble media; tubal surgery before in vitro fertilisation.

QUESTIONS

INTERVENTIONS

Covered elsewhere in Clinical Evidence

See erectile dysfunction

See fibroids

See pelvic inflammatory disease

See varicocele

See endometriosis

See polycystic ovary syndrome

Footnote

*No RCTs, but strong observational evidence that in vitro fertilisation increases live birth rates.

Key points

- About 17% of couples in industrialised countries seek help for infertility, which may be caused by ovulatory failure, tubal damage or endometriosis or a low sperm count.
- In women with infertility, in vitro fertilisation may be as likely to lead to pregnancy as intracytoplasmic sperm injection, but increases the risks of multiple pregnancy.

  Gonadotrophin releasing hormone agonists also increase pregnancy rates, but gonadotrophin releasing hormone antagonists may be less effective.

  Intrauterine insemination plus controlled ovarian stimulation is considered to be beneficial in women with unexplained infertility or cervical hostility.
- In women with ovulatory disorders, clomifene and tamoxifen increase ovulation and pregnancy rates, and metformin increases ovulation rates.

  Gonadotrophins may increase pregnancy rates but may increase the risk of ovarian cancer, ovarian hyperstimulation syndrome and multiple pregnancy.

  Laparoscopic ovarian drilling may be as effective as gonadotrophins.

  We don't know whether cyclofenil, pulsed gonadotrophin releasing hormone, gonadotrophin priming of oocytes before in vitro maturation, or ovarian wedge biopsy increase pregnancy rates compared with no treatment.
- In women with tubal infertility, tubal flushing increases pregnancy rates, with oil soluble media possibly more effective than water soluble media.

  Tubal surgery before in vitro fertilisation may increase pregnancy rates compared with no treatment in women with hydrosalpinges, but we don't know whether selective salpingography plus tubal catheterisation is beneficial.
- In women with endometriosis, adding gonadotrophins to intrauterine insemination increases live birth rates compared with intrauterine insemination alone.

  Laparoscopic ablation of endometrial deposits may increase live birth rates compared with diagnostic laparoscopy.

  Drugs to induce ovarian suppression may not increase pregnancy rates.

DEFINITION

This review focuses on infertility related to factors associated with the woman rather than the man. Normal fertility has been defined as achieving a pregnancy within 2 years by regular unprotected sexual intercourse. [1] However, many define infertility as the failure to conceive after 1 year of unprotected intercourse. Infertility can be primary, in women who have never conceived, or secondary, in women who have previously conceived. This review will deal with infertility owing to endometriosis, ovulation disorders, and tubal infertility. Endometriosis is a progressive disease which occurs when the endometrial tissue lining the uterus grows outside the uterus and attaches to the ovaries, fallopian tubes, or other organs in the abdominal cavity (See endometriosis). Ovulation disorders are defined by the failure of an ovum to be expelled because of a malfunction in the ovary, and are a major cause of infertility. Tubal infertility is the inability to conceive owing to a blockage in one or both fallopian tubes, and is a common cause of infertility.

INCIDENCE/ PREVALENCE

Although there is no evidence of a major change in the prevalence of female infertility, many more couples are seeking help than previously. Currently, about 1/6 (17%) couples in industrialised countries will seek medical advice for infertility. [2] Rates of primary infertility vary widely between countries, ranging from < 6% in China, Malawi, Tanzania, and Zambia; 9% in the Philippines; > 10% in Finland, Sweden, and Canada; and 18% in Switzerland. [3] [4] Reported rates of secondary infertility are less reliable.

AETIOLOGY/ RISK FACTORS

In the UK, about 10–20% of infertility cases are unexplained. [5] The rest are caused by ovulatory failure (27%), tubal damage (14%), endometriosis (5%), low sperm count or quality (19%), and other causes (5%). [6]

PROGNOSIS

In developed countries, 80–90% of couples attempting to conceive are successful after 1 year and 95% after 2 years. [7] The chances of becoming pregnant vary with the cause and duration of infertility, the woman's age, the woman's previous pregnancy history, and the availability of different treatment options. [8] [9] For the first 2–3 years of unexplained infertility, cumulative conception rates remain high (27–46%) but decrease with increasing age of the woman and duration of infertility. [9] The background rates of spontaneous pregnancy in infertile couples can be calculated from longitudinal studies of infertile couples who have been observed without treatment. [9]

AIMS OF INTERVENTION

To achieve the delivery of one healthy baby; to reduce the distress associated with infertility, with minimal adverse effects.

OUTCOMES Live births, miscarriages, multiple pregnancies, incidence of ovarian hyperstimulation syndrome, satisfaction with services and treatments, acceptance of childlessness if treatment is unsuccessful. Pregnancy and ovulation rates are important intermediate outcomes. Spontaneous pregnancies can occur without treatment in couples who are considered infertile. [9] Effectiveness of treatments for infertility should be assessed on the basis of pregnancy rates over and above the spontaneous pregnancy rates otherwise the impacts of treatments may be overestimated.

METHODS *Clinical Evidence* search and appraisal April 2004. **Crossover design:** For infertility, RCTs with a crossover design may overestimate the treatment effect because pregnancies occurring in the first half of the trial will remove couples from the second half. [10] Crossover trials were included in some systematic reviews where no or few RCTs using a parallel group design were available. Ideally, only data from the first half of the trial, before crossover, should be used. However, post-crossover results are reported in the absence of pre-crossover results. However, a study that used a computer model to compare the results of crossover and parallel designed trials suggests that any overestimation may be clinically irrelevant. [11] We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 26).

QUESTION What are the effects of treatments for infertility caused by ovulation disorders?

OPTION CLOMIFENE

Pregnancy rate

Compared with placebo Clomifene increases pregnancy rates compared with placebo in women with infrequent ovulation (high-quality evidence).

Compared with tamoxifen Clomifene may be as effective as tamoxifen at increasing pregnancy rates at 9 months in anovulatory women (low-quality evidence).

Compared with clomifene plus metformin Clomifene alone is less effective than clomifene plus metformin at increasing pregnancy rates at 6 months in women with polycystic ovary disease (high-quality evidence).

Compared with pulsatile gonadotrophin-releasing hormone Clomifene may be as effective as pulsatile gonadotrophin-releasing hormone plus GnRH agonist at increasing pregnancy rates in women with polycystic ovary syndrome (low-quality evidence).

Adverse effects

Clomifene seems not to increase the risk of ovarian cancer in women with infertility (very low-quality evidence). Clomifene is associated with increased risks of multiple pregnancy.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Clomifene versus placebo:

We found one systematic review (search date not reported, 4 crossover RCTs, 347 cycles evaluated) which compared clomifene (clomiphene) 10–200 mg versus placebo in women who ovulate infrequently. [12] It found that clomifene significantly increased pregnancy rates compared with placebo (2 RCTs; post-crossover pregnancy rate: 13/96 [13%] with clomifene *v* 4/96 [4%] with placebo; RR 3.00, 95% CI 1.10 to 8.16). It also found that clomifene significantly increased ovulation rates compared with placebo (4 RCTs; post-crossover ovulation rate: 86/142 [61%] with clomifene *v* 33/137 [22%] with placebo; RR 2.49, 95% CI 1.80 to 3.44).

Clomifene versus tamoxifen:

We found two RCTs. [13] [14] The first RCT (86 anovulatory women aged < 40 years) compared clomifene (maximum daily dose 150 mg, 91 treatment cycles evaluated) versus tamoxifen (maximum daily dose 60 mg, 113 treatment cycles evaluated). [13] It found no significant difference between clomifene and tamoxifen in the overall rate of ovulation or in the number of pregnancies (overall ovulation rate: 41/91 [45%] with clomifene *v* 50/113 [44%] with tamoxifen; P > 0.05; see comment below; number of pregnancies: 6/40 [15%] with clomifene *v* 10/46 [22%] with tamoxifen; P > 0.05). The second RCT (66 anovulatory women) also compared clomifene versus tamoxifen. It found no difference between treatments in pregnancy rate at 9 months (pregnancy rate: 80% in both groups; P value not reported). [14]

Clomifene versus clomifene plus tamoxifen:

We found one randomised crossover trial (20 anovulatory women) which compared clomifene (100 mg during cycle days 5–9 for 3 consecutive treatment cycles) versus clomifene plus tamoxifen (clomifene 50 mg plus tamoxifen 20 mg during cycle days 5–9 for 3 consecutive treatment cycles). [15] It found that clomifene plus tamoxifen significantly improved the pre-crossover ovulation rate

per cycle compared with clomifene alone at the end of three treatment cycles (12/30 [40.0%] with clomifene *v* 22/28 [78.6%] with clomifene plus tamoxifen; P < 0.01). [15]

Clomifene versus clomifene plus metformin:
We found one systematic review (search date 2002, 3 RCTs, 173 women with polycystic ovary syndrome, many of whom had not responded during previous treatment with clomifene). [16] The review found that clomifene plus metformin significantly increased pregnancy rates over 6 months compared with clomifene alone (3 RCTs; 6/85 [7%] with clomifene *v* 25/88 [28%] with clomifene plus metformin; OR 4.40, 95% CI 1.96 to 9.85). It also found that clomifene plus metformin significantly increased ovulation rates compared with clomifene alone (3 RCTs: 36/85 [42%] with clomifene *v* 67/88 [76%] with clomifene plus metformin; OR 4.41, 95% CI 2.37 to 8.22). [16]

Clomifene versus pulsatile gonadotrophin releasing hormone:
See benefits of pulsatile gonadotrophin releasing hormone, p 11 .

Harms:

Clomifene versus placebo:
The systematic review gave no information on adverse effects. [12]

Multiple pregnancy:
Multiple pregnancy occurs in 2–13% of women with all causes of infertility taking clomifene compared with a spontaneous multiple pregnancy rate of about 1–2% of women in North American and European populations. [17] [18] In a 1 year survey in the UK, 25/44 (57%) triplet pregnancies reported were attributable to clomifene. [19] Clomifene was also implicated in 2/8 (25%) sets of quadruplets and quintuplets reported.

Ovarian hyperstimulation syndrome:
Clomifene tends to cause only mild ovarian hyperstimulation that does not require treatment. Severe ovarian hyperstimulation syndrome is very rare after clomifene treatment; the author is aware of four case reports worldwide.

Ovarian cancer:
One cohort study (3837 infertile women, both with and without ovarian abnormalities) found that the observed incidence of ovarian cancer in women taking clomifene was about three times greater than the expected incidence for the general population (standardised incidence ratio: 3.1, 95% CI 1.4 to 5.9). [20] However, a second cohort study (29 700 women, of whom 1422 had ovarian defects and 1182 were treated with clomifene) found no significant difference between the observed incidence of ovarian cancer in women treated with clomifene and the expected incidence in the general population (standardised incidence ratio: 2.46, 95% CI 0.35 to 17.5). [21] Two case control studies also found no association between exposure to clomifene and the risk of developing ovarian cancer: 9/64 (14%) cases *v* 11/58 (19%) controls; adjusted OR = 0.67, 95% CI 0.23 to 1.96; [22] and 200 cases (11/200 [6%]) *v* 408 area matched controls (18/408 [4%]); adjusted OR 0.88, 95% CI 0.33 to 2.34). [23]

Clomifene versus clomifene plus tamoxifen:
The RCT found that all pregnancies were normal and single, and no severe complications were associated with either of the treatments (no further data reported). [15]

Clomifene versus tamoxifen:
The RCTs gave no information on adverse effects. [13] [14]

Clomifene versus clomifene plus metformin:
The systematic review gave no information on adverse effects. [16]

Clomifene versus pulsatile gonadotrophin releasing hormone:
See harms of pulsatile gonadotrophin releasing hormone, p 11 .

Comment:

Clomifene versus tamoxifen:
Both RCTs comparing clomifene versus tamoxifen based estimates of pregnancy rates on fewer than 30 pregnancies. [13] [14]

Ovarian cancer:
In the cohort study, 5/11 (45%) people with ovarian cancer were diagnosed with borderline epithelial tumours that had low malignant potential, and two with granulosa cell tumours that had different embryological, pathological, and epidemiological features from epithelial tumours. [20] Borderline and malignant tumours pose different risks that are not easy to combine and excluding the two granulosa cell tumours from the number of ovarian cancers found diminishes the increased risk attributed to clomifene treatment.

Clomifene versus clomifene plus metformin:
The RCTs identified by the review did not assess live birth rate or clinical pregnancy rate as a primary outcome measure. [16]

OPTION TAMOXIFEN

Pregnancy rate
Compared with clomifene Tamoxifen may be as effective as clomifene at increasing pregnancy rates at 9 months in anovulatory women (low-quality evidence).

Note
We found no direct information about whether tamoxifen is better than no active treatment in women with infertility.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Tamoxifen versus placebo:
We found no systematic review or RCTs.

Tamoxifen versus clomifene (clomiphene):
We found two RCTs. [13] [14] See benefits of clomifene, p 3 .

Harms:

Tamoxifen versus placebo:
We found no systematic review or RCTs (see harms of tamoxifen in metastatic breast cancer and non-metastatic breast cancer).

Tamoxifen versus clomifene:
See harms of clomifene, p 3 .

Comment: None.

OPTION METFORMIN

Live birth rate
Compared with placebo Metformin may be no more effective than placebo at increasing live birth rates in women with polycystic ovary syndrome (low-quality evidence).

Pregnancy rate
Compared with placebo Metformin may be no more effective than placebo at increasing pregnancy rates in women with polycystic ovary syndrome (low-quality evidence).

Metformin plus clomifene compared with clomifene alone Metformin plus clomifene is more effective than clomifene alone at increasing pregnancy rates at 6 months in women with polycystic ovary disease (high-quality evidence).

Compared with laparoscopic ovarian drilling Metformin may be no more effective than laparoscopic ovarian drilling at increasing pregnancy rates in women with clomifene-resistant polycystic ovary syndrome (very low-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Metformin versus placebo:
We found one systematic review (search date 2002, 13 RCTs). [16] The review found that metformin significantly increased ovulation rates compared with placebo (7 RCTs; 72/156 [46%] with metformin *v* 37/154 [24%] with placebo; RR 1.96, 95% CI 1.47 to 2.61). However, the review found no significant difference between metformin and placebo in live birth or pregnancy rates (live birth rate: 2 RCTs; 2/25 [8%] in both groups; RR 1.00, 95% CI 0.19 to 5.24; pregnancy rate: 5 RCTs; 9/87 [10.3%] with metformin *v* 3/85 [3.5%] with placebo; RR 2.25, 95% CI 0.77 to 6.52). [16] The review is likely to have been underpowered to detect a clinically important difference in these outcomes because of low event rates in the RCTs identified.

Metformin plus clomifene versus clomifene alone:
See benefits of clomifene, p 3 .

Metformin versus laparoscopic ovarian drilling:
See benefits of laparoscopic ovarian drilling, p 10 .

Harms:

Metformin versus placebo:
The review found that metformin significantly increased gastrointestinal disturbance, other than nausea and vomiting, compared with placebo (19/65 [29%] with metformin *v* 5/68 [7%] with placebo;

RR 3.48, 95% CI 1.49 to 8.10). [16] The RCTs identified by the review reported no miscarriages or multiple pregnancies.

Metformin plus clomifene versus clomifene alone:
See harms of clomifene, p 3 .

Metformin versus laparoscopic ovarian drilling:
See harms of laparoscopic ovarian drilling, p 10 .

Comment: **Metformin versus placebo:**
None of the RCTs identified by the review assessed live birth rate or clinical pregnancy rate as a primary outcome measure. [16]

OPTION CYCLOFENIL

Pregnancy rate
Compared with placebo Cyclofenil is no more effective than placebo at increasing pregnancy rates at 3 months in women with ovulatory disorders (moderate-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits: **Cyclofenil versus placebo:**
We found one RCT (213 women with either ovulatory disorders or unexplained infertility) which compared three cycles of cyclofenil (800 mg daily from days 4–8 of the ovulatory cycle) versus placebo (see comment below). [24] It found no significant difference between treatments in the cumulative pregnancy rate (26/114 [23%] with cyclofenil *v* 21/99 [21%] with placebo; P = 0.77).

Harms: The RCT gave no information on adverse effects. [24]

Comment: Only 123/213 (58%) women in the RCT had ovulatory disorders and the results for these women were not presented separately. [24] The RCT does not, therefore, exclude a possible benefit of cyclofenil.

OPTION GONADOTROPHINS

Pregnancy rate
Human menopausal gonadotrophin compared with urinary follicle-stimulating hormone Human menopausal gonadotrophin is as effective as urinary follicle stimulating hormone at increasing pregnancy rates in women with polycystic ovary syndrome (moderate-quality evidence).

Human menopausal gonadotrophin compared with recombinant follicle stimulating hormone Human menopausal gonadotrophin is as effective as recombinant follicle-stimulating hormone at increasing pregnancy rates in women having in vitro fertilisation treatment (moderate-quality evidence).

Recombinant follicle-stimulating hormone compared with urinary follicle-stimulating hormone Recombinant follicle-stimulating hormone is as effective as urinary follicle stimulating hormone at increasing pregnancy rates in women with clomifene-resistant anovulation (moderate-quality evidence).

Compared with laparoscopic ovarian drilling Gonadotrophins are as effective as laparoscopic ovarian drilling at increasing pregnancy rates at 6–12 months in women with clomifene-resistant polycystic ovary syndrome (moderate-quality evidence).

Note
We found no clinically important results about the effects of gonadotrophins compared with no active treatment or clomifene (clomiphene).

Adverse effects
Gonadotrophins may be associated with an increased risk of epithelial ovarian cancer compared with controls (low-quality evidence). Gonadotrophins have been associated with ovarian hyperstimulation syndrome and multiple pregnancies.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits: **Gonadotrophins versus placebo or clomifene (clomiphene):**
We found no RCTs.

Human menopausal gonadotrophins versus urinary follicle stimulating hormone (urofollitropin):
We found one systematic review (search date not reported), which compared human menopausal gonadotrophin (hMG) versus urofollitropin in women with polycystic ovary syndrome. [25] It found no significant difference between treatments in pregnancy rate or ovulation rate per cycle (pregnancy rate, 4 RCTs: 19/183 [10%] with urofollitropin *v* 26/213 [12%] with hMG; RR 0.84, 95% CI 0.48 to 1.46; ovulation rate, 6 RCTs: 190/266 [71%] with urofollitropin *v* 206/269 [77%] with hMG; RR 0.91, 95% CI 0.83 to 1.01).

Human menopausal gonadotrophins versus recombinant follicle stimulating hormone (follitropin):
We found one systematic review (search date 2002, 8 RCTs) which compared hMG (with hMG pituitary downregulation using the long protocol) versus follitropin in women having ovarian stimulation during in vitro fertility treatment. [26] The review found no significant difference between hMG and follitropin in the combined outcome of ongoing pregnancy or live birth per woman (4 RCTs; 167/611 [27%] with hMG *v* 139/603 [23%] with follitropin; RR 1.19, 95% CI 0.98 to 1.45).

Recombinant follicle stimulation hormone (follitropin) versus urinary follicle stimulation hormone (urofollitropin):
We found one systematic review (search date 2000, 3 RCTs, 457 women with clomifene resistant, normogonadotrophic anovulation), which compared follitropin versus urofollitropin. [27] Follitropin or urofollitropin was given for 1–3 cycles with a cut off point of 5–6 weeks of treatment. The review found no significant difference between follitropin and urofollitropin in pregnancy rate per woman or ovulation rate per cycle (pregnancy rate, 3 RCTs: 86/231 [37%] with follitropin *v* 86/214 [40%] with urofollitropin; RR 0.97, 95% CI 0.77 to 1.23; ovulation rate, 2 RCTs: 182/255 [71%] with follitropin *v* 142/202 [70%] with urofollitropin; RR 1.05, 95% CI 0.93 to 1.19).

Gonadotrophins versus laparoscopic ovarian drilling:
See benefits of laparoscopic ovarian drilling, p 10 .

Harms:

Gonadotrophins versus placebo or clomifene:
We found no RCTs.

Human menopausal gonadotrophins versus urinary follicle stimulation hormone (urofollitropin):
The systematic review found no significant difference between hMG and urofollitropin in miscarriage or multiple pregnancy rates (miscarriage: 4 RCTs; 7/22 [32%] with urofollitropin *v* 10/25 [40%] with hMG; RR 0.90, 95% CI 0.43 to 1.89; multiple pregnancy: 4 RCTs; 2/22 [9%] *v* 4/28 [14%]; RR 0.68, 95% CI 0.18 to 2.61). [25] It also found that the risk of ovarian hyperstimulation syndrome (OHSS) was significantly lower with urofollitropin compared with hMG (5 RCTs; 6/153 [4%] with urofollitropin *v* 20/151 [13%] with hMG; RR 0.26, 95% CI 0.12 to 0.58).

Ovarian cancer:
One case control study (200 women with ovarian cancer and 408 area matched controls) found that women with epithelial ovarian cancer were about three times more likely to have been exposed to hMG alone compared with controls (adjusted OR: 3.19, 95% CI 0.86 to 11.82). [23] This study had methodological weaknesses. The previous treatment with ovulation induction agents, including hMGs, was determined by interview using a standard questionnaire and was not confirmed by medical records. The association between the use of hMG and ovarian cancer should be interpreted with caution as the results may be subject to recall bias.

Human menopausal gonadotrophins versus recombinant follicle stimulating hormone (follitropin):
The systematic review found no significant difference between hMGs (downregulation using the long protocol) and follitropin in the rate of miscarriage, multiple pregnancy, or OHSS per woman (miscarriage, 4 RCTs: 22/611 [3.6%] with hMG *v* 19/603 [3.2%] with follitropin; RR 1.17, 95% CI 0.64 to 2.12; multiple pregnancy, 4 RCTs: 65/583 [11%] *v* 45/565 [8%]; RR 1.40, 95% CI 0.98 to 2.01; OHSS, 4 RCTs: 10/611 [1.6%] *v* 6/603 [1.0%]; RR 1.61, 95% CI 0.59 to 4.40). [26]

Recombinant follicle stimulating hormone (follitropin) versus urinary follicle stimulation hormone (urofollitropin):
The systematic review found no significant difference between follitropin and urofollitropin in the per pregnancy rates of miscarriage, multiple pregnancy, or OHSS (miscarriage: 20/86 [23%] with follitropin *v* 15/86 [17%] with urofollitropin; OR 1.26, 95% CI 0.59 to 2.70; multiple pregnancy: 5/86 [6%] *v* 12/86 [14%]; OR 0.44, 95% CI 0.16 to 1.21; OHSS: 9/231 [4%] *v* 4/214 [2%]; OR 1.55, 95% CI 0.50 to 4.84). [27]

Multiple pregnancy:
One case series (41 women) found that multiple pregnancy occurred in 36% (absolute figures not clear) of women with polycystic ovary syndrome when conventional regimens of gonadotrophins (hMG-hCG) were used to induce ovulation. [28]

Comment:

Clinical guide:
Despite not being placebo controlled, trials in the review of gonadotrophins often included women who were not ovulating and, therefore, provide some evidence that treatment is effective. [25] Follitropin is not derived from human tissues.

OPTION GONADOTROPHIN RELEASING HORMONE (GNRH) AGONISTS PLUS GONADOTROPHINS

Pregnancy rate
Compared with gonadotrophins alone Gonadotrophin-releasing hormone agonists plus gonadotrophins increase pregnancy rates compared with gonadotrophins alone in women with various causes of infertility having in vitro fertilisation (moderate-quality evidence).

Depot gonadotrophin-releasing hormone agonists compared with daily gonadotrophin-releasing hormone agonists Depot gonadotrophin-releasing hormone agonists are as effective at increasing pregnancy rates compared with daily gonadotrophin-releasing hormone agonists (high-quality evidence).

Long protocol gonadotrophin-releasing hormone agonist compared with short or ultrashort protocols Long protocol gonadotrophin-releasing hormone agonist increases pregnancy rates comapred with short or ultrashort protocols (high-quality evidence).

Intranasal route compared with other routes Gonadotrophin-releasing hormone agonists given intranasally are as effective at increasing pregnancy rates as those given by other routes (moderate-quality evidence).

Adverse effects
Gonadotrophin agonists plus gonadotrophin combination treatments are associated with an increased risk of ovarian hyperstimulation and multiple pregnancy.

Note
We found no clinically important results about the effects of gonadotrophin-releasing hormone agonists plus gonadotrophins compared with gonadotrophin-releasing hormone antagonists.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Gonadotrophin releasing hormone agonists plus gonadotrophins versus gonadotrophins alone:
We found no systematic review or RCTs in women with ovulation disorders. We found one systematic review (search date not reported, 10 RCTs in women with various causes of infertility, all having in vitro fertility treatment; 1636 cycles analysed). [29] The review compared gonadotrophin releasing hormone agonists (GnRH agonists) plus gonadotrophins versus gonadotrophins alone (human GnRH or follicle stimulating hormone [FSH]), or versus clomifene (clomiphene) plus gonadotrophins. It found that GnRH agonists plus gonadotrophins significantly increased clinical pregnancy rate per cycle compared with gonadotrophins alone (OR 1.80, 95% CI 1.33 to 2.44).

Gonadotrophin releasing hormone agonists plus gonadotrophins versus gonadotrophin-releasing hormone antagonists:
We found no systematic review or RCTs.

Depot versus daily dose:
One systematic review (search date not reported, 6 RCTs, 552 women) found no significant difference between depot GnRH agonist and daily GnRH agonist in clinical pregnancy rate per woman, ongoing pregnancy rate per cycle, multiple pregnancy rate, miscarriage rate, or incidence of OHSS (pregnancy rate: 75/263 [29%] with depot *v* 88/289 [30%] with daily; RR 0.96, 95% CI 0.74 to 1.24; ongoing pregnancy rate per cycle: 45/195 [23%] *v* 51/197 [26%]; RR 0.89, 95% CI 0.63 to 1.26; multiple pregnancy rate: 45/195 [23%] *v* 51/197 [26%]; RR 0.89, 95% CI 0.63 to 1.26; miscarriage rate: 9/55 [16%] *v* 9/60 [14%]; RR 1.14, 95% CI 0.50 to 2.60; incidence of OHSS: 2/77 [3%] *v* 3/78 [4%]; RR 0.73, 95% CI 0.15 to 3.55). [30]

Long versus short or ultrashort protocol:
We found one systematic review (search date not reported, 26 RCTs), which found that the long GnRH agonist protocol significantly increased the clinical pregnancy rate per cycle compared with short or ultrashort GnRH agonist protocols (pregnancy rate per cycle: pooled OR 1.32, 95% CI 1.10 to 1.57). [31]

Intranasal versus other routes of administration:
One systematic review (search date not reported, 9 RCTs, 1014 women having in vitro fertility treatment for 12–100 cycles) found no significant difference between intranasal GnRH agonist and other routes of administration of GnRH agonists in clinical pregnancy rate per embryo transfer (4 RCTs; OR 0.93, 95% CI 0.57 to 1.51). There were no data on pregnancy rate per cycle. [32]

Harms:

Gonadotrophin releasing hormone agonists plus gonadotrophins versus gonadotrophins alone:
The systematic review found that GnRH agonists plus gonadotrophins significantly increased the risk of multiple pregnancies compared with gonadotrophins alone (5 RCTs; OR 2.56, 95% CI 0.95 to 6.91). [29]

Gonadotrophin releasing hormone agonists plus gonadotrophins versus gonadotrophin releasing hormone antagonists:
When gonadotrophins were used concomitantly with GnRH antagonists in women with polycystic ovary syndrome, the risk of ovary hyperstimulation syndrome (OHSS) was significantly increased (OR 3.15; 95% CI 1.48 to 6.70). [33] No conclusions could be drawn about miscarriage and multiple pregnancy rates owing to insufficient data. See harms of gonadotrophin releasing hormone antagonists, p 9 .

Comment:

Clinical guide:
GnRH agonists plus gonadotrophin combination treatments are not widely used in ovulation induction treatment for ovulatory disorders because it does not improve pregnancy rates, and is associated with an increased risk of ovarian hyperstimulation. [33] GnRH agonists are most often used in conjunction with gonadotrophins to achieve pituitary downregulation and facilitate cycle control in ovarian stimulation during in vitro fertilisation treatment.

OPTION GONADOTROPHIN RELEASING HORMONE (GNRH) ANTAGONISTS

Pregnancy rates
Compared with gonadotrophin-releasing hormone agonists Gonadotrophin-releasing hormone antagonists are less effective than gonadotrophin-releasing hormone agonists at increasing pregnancy rates in couples being treated for infertility (including infertility owing to male factor infertility, but excluding women with polycystic ovary syndrome) (moderate-quality evidence).

Note
We found no clinically important results about the effects of gonadotrophin-releasing hormone antagonists compared with no active treatment, or with gonadotrophin-releasing hormone agonists plus gonadotrophins in women with infertility caused by ovulation disorders.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Gonadotrophin releasing hormone antagonists versus placebo or other treatments:
We found no RCTs.

Gonadotrophin releasing hormone antagonists versus gonadotrophin releasing hormone agonists:
We found no systematic review or RCTs which compared gonadotrophin releasing hormone (GnRH) antagonists versus GnRH agonists in women with infertility caused by ovulation disorders (see comment below).

Gonadotrophin releasing hormone antagonists versus gonadotrophin releasing hormone agonists plus gonadotrophins:
We found no systematic review or RCTs.

Harms:

Gonadotrophin releasing hormone antagonists versus placebo or other treatments:
We found no RCTs.

Gonadotrophin releasing hormone antagonists versus gonadotrophin releasing hormone agonists:
We found no RCTs (see comment below).

Gonadotrophin releasing hormone antagonists versus gonadotrophin releasing hormone agonists plus gonadotrophins:
We found no systematic review or RCTs.

Comment: We found one systematic review (search date 2001, 5 RCTs, 1796 women). [34] The review included couples being treated for infertility (including infertility owing to male factor infertility), but excluded women with polycystic ovary syndrome. The review compared GnRH antagonists (0.25 mg multiple low dose regimen [4 RCTs] or 3 mg single high dose regimen [1 RCT]) versus GnRH agonists (long protocol). It found that GnRH antagonists significantly reduced clinical pregnancy rates per woman compared with GnRH agonists (pooled OR 0.79, 95% CI 0.63 to 0.99).

Harms:
The review found no significant difference between treatments in multiple pregnancy rates (pooled OR 0.74, 95% CI 0.48 to 1.16), the incidence of severe ovarian hyperstimulation syndrome (pooled OR 0.47, 95% CI 0.18 to 1.25), or miscarriage rate (pooled OR 1.03, 95% CI 0.52 to 2.04). [34]

OPTION LAPAROSCOPIC OVARIAN DRILLING

Pregnancy rate
Compared with metformin Laparoscopic ovarian drilling may be no more effective than metformin at increasing pregnancy rates in women with clomifene-resistant polycystic ovary syndrome (very low-quality evidence).

Compared with gonadotrophins Laparoscopic ovarian drilling is no more effective than gonadotrophins at increasing pregnancy rates at 6–12 months in women with clomifene-resistant polycystic ovary syndrome (moderate-quality evidence).

Adverse effects
Laparoscopic ovarian drilling has been associated with lower risks of multiple pregnancy compared with gonadotrophins, and lower risks of adhesions compared with ovarian wedge biopsy.

Note
We found no direct information about whether laparoscopic ovarian drilling is better than no active treatment.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Laparoscopic ovarian drilling versus no treatment:
We found no RCTs.

Laparoscopic ovarian drilling versus gonadotrophins:
We found one systematic review (search date 2001, 4 RCTs, 303 women with anovulatory clomifene [clomiphene] resistant polycystic ovary syndrome (PCOS)) [35] and two subsequent RCTs [36] [37] which compared laparoscopic ovarian drilling versus gonadotrophins (see comment below). The review found no significant difference between laparoscopic ovarian drilling and gonadotrophins in pregnancy rates after 6–12 months' follow up (81/127 [64%] with laparoscopic ovarian drilling *v* 72/126 [57%] with gonadotrophins; OR 1.42, 95% CI 0.84 to 2.42). [35] The first subsequent RCT (18 women with clomifene or purified follicle stimulating hormone resistant PCOS) compared laparoscopic ovarian drilling versus a gonadotrophin releasing hormone analogue plus a combined oral contraceptive. [36] All the women also received three cycles of follitropin plus intrauterine insemination. The RCT found no significant difference in the number of pregnancies or live births after 6 months' treatment (pregnancies: 5/10 [50%] with laparoscopic ovarian drilling *v* 5/8 [63%] with gonadotrophin releasing hormone analogue plus combined oral contraceptive; reported as not significant; P value not reported; live births: 5/10 [50%] with laparoscopic ovarian drilling *v* 4/8 [50%] with gonadotrophin releasing hormone analogue plus combined oral contraceptive; reported as not significant; P value not reported). [36] The second subsequent RCT (50 women with clomifene resistant polycystic ovarian syndrome) compared laparoscopic ovarian drilling versus gonadotrophins for three cycles. [37] It found no significant difference in ongoing pregnancy rate between ovarian drilling and gonadotrophins at the end of 6 months' follow up (8/29 [28%] with ovarian laser drilling *v* 7/21 [33%] with gonadotrophins; RR 0.82, 95% CI 0.36 to 1.93).

Laparoscopic ovarian drilling versus metformin:
We found one RCT (161 women with clomifene resistant PCOS) which found no significant difference between laparoscopic drilling and metformin in pregnancy or ovulation rates (pregnancy: 58/97 [60%] with laparoscopic drilling *v* 41/64 [64%] with metformin; ovulation rate: 81/97 [84%] *v* 51/64 [80%]; results reported stated as non-significant for both outcomes; P values not reported). [38]

Harms:

Laparoscopic ovarian drilling versus gonadotrophins:
The systematic review found that laparoscopic ovarian drilling significantly reduced rates of multiple pregnancies compared with gonadotrophins (OR 0.16, 95% CI 0.03 to 0.98). [35] The first subsequent RCT reported no miscarriages with laparoscopic ovarian drilling and one miscarriage with gonadotrophin releasing hormone analogue plus combined oral contraceptive. It gave no further information on adverse effects. [26] The second subsequent RCT reported three miscarriages in each

treatment group, and no multiple pregnancies in either group. [37] The RCT also found no major complications associated with laparoscopic ovarian drilling and no cases of ovarian hyperstimulation syndrome (OHSS) in the gonadotrophin treated group. One person in the gonadotrophin treated group developed severe cystic acne. Adverse effects associated with laparoscopic ovarian drilling include the risks of general anaesthesia, postoperative adhesion formation, [39] and pelvic infection. [40] We found no evidence to support the suggestion that laparoscopic drilling increases the long term risk of premature ovarian failure. Laparoscopic drilling is thought not to increase the risk of multiple pregnancies as it usually induces spontaneous ovulation, in contrast to the multifollicular ovulation that may be induced by the use of gonadotrophins.

Laparoscopic ovarian drilling versus metformin:
The RCT found no significant difference between laparoscopic ovarian drilling and metformin in the rates of multiple pregnancy, OHSS, or ectopic pregnancy (multiple pregnancy: 4/58 [7%] with ovarian drilling *v* 2/41 [5%] with metformin; OHSS: 2/58 [3%] *v* 1/41 [2%]; ectopic pregnancy: 3/58 [5%] *v* 1/41 [2%]; all outcomes reported as non-significant; P values not reported). [38]

Comment:

Clinical guide:
The trials of laparoscopic ovarian drilling included women who were not ovulating and, therefore, provide some evidence that treatment is effective despite the lack of placebo controls. [35] [36]

OPTION PULSATILE GONADOTROPHIN RELEASING HORMONE

Pregnancy rate
Compared with clomifene Pulsatile gonadotrophin-releasing hormone plus GnRH agonist may be no more effective than clomifene at increasing pregnancy rates in women with polycystic ovary syndrome (low-quality evidence).

Note
We found no clinically important results about the effects of pulsatile gonadotrophin-releasing hormone compared with human menopausal gonadotrophin, about pulsatile gonadotrophin-releasing hormone plus follicle-stimulating hormone compared with follicle-stimulating hormone alone, or about pulsatile gonadotrophin-releasing hormone plus gonadotrophin-releasing hormone agonist compared with pulsatile gonadotrophin-releasing hormone alone.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Pulsatile gonadotrophin releasing hormone versus clomifene (clomiphene):
We found one systematic review (search date 2003, 1 RCT, 28 women with polycystic ovary syndrome). [41] The RCT compared pulsatile gonadotrophin releasing hormone (GnRH; 10–20 µg iv every 90 minutes) immediately after pretreatment with a GnRH agonist (400 µg intranasally for 3 weeks) versus clomifene (50 mg started on cycle day 3–7). It found no significant difference between treatments in pregnancy rate per woman or ovulation rate per cycle (pregnancy: 4/16 [25%] with pulsatile GnRH after GnRH agonist *v* 4/12 [33%] with clomifene; OR 0.67, 95% CI 0.13 to 3.43; ovulation: 19/40 [47%] with pulsatile GnRH after GnRH agonist *v* 15/25 [60%] with clomifene; OR 0.61, 95% CI 0.23 to 1.65; see comment below).

Pulsatile gonadotrophin releasing hormone versus human menopausal gonadotrophin alone:
We found one systematic review (search date 2003, 1 crossover RCT, 9 women with clomifene resistant polycystic ovary syndrome). [41] The RCT compared pulsatile GnRH versus human menopausal gonadotrophin (hMG), however the RCT was too small to meet *BMJ Clinical Evidence* inclusion criteria.

Pulsatile gonadotrophin releasing hormone plus follicle stimulating hormone versus follicle stimulating hormone alone:
We found one systematic review (search date 2003, 1 crossover RCT, 8 clomifene resistant women with oligomenorrhoea and infertility for at least 3 years). [41] The RCT compared pulsatile gonadotrophin plus follicle stimulating hormone (FSH) versus FSH alone, however the RCT was too small to meet *Clinical Evidence* inclusion criteria.

Pulsatile gonadotrophin releasing hormone plus gonadotrophin releasing hormone agonist versus pulsatile gonadotrophin releasing hormone alone:
We found one systematic review (search date 2003, 1 crossover RCT, 12 women with oligo- or amenorrhoea). [41] The RCT compared pulsatile GnRH after pretreatment with a GnRH agonist versus pulsatile GnRH alone, however the RCT was too small to meet *Clinical Evidence* inclusion criteria.

Harms:

Pulsatile gonadotrophin releasing hormone versus clomifene:
The RCT identified by the systematic review found no cases of OHSS or multiple pregnancy per woman in either treatment group, see comment below. [41]

Pulsatile gonadotrophin releasing hormone versus human menopausal gonadotrophin alone:
The RCT identified by the systematic review did not meet *BMJ Clinical Evidence* inclusion criteria. [41]

Pulsatile gonadotrophin releasing hormone plus follicle stimulating hormone versus follicle stimulating hormone alone:
The RCT identified by the systematic review did not meet *BMJ Clinical Evidence* inclusion criteria. [41]

Pulsatile gonadotrophin releasing hormone plus gonadotrophin releasing hormone agonist versus pulsatile gonadotrophin releasing hormone alone:
The RCT identified by the systematic review did not meet *BMJ Clinical Evidence* inclusion criteria. One retrospective analysis (229 cycles in 71 women) compared pulsatile GnRH versus gonadotrophins alone and found no significant difference in multiple pregnancy rates after six cycles. [41] However, 75% of the multiple pregnancies in the gonadotrophin group were triplets or higher order multiple pregnancies, whereas all multiple pregnancies in the GnRH group were twins.

Comment:

Case series (256 anovulatory women with hypogonadotropic hypogonadism having 1043 treatment cycles) found cumulative pregnancy rates of 59–73% at 6 months and 81–92% at 12 months. [42] [43] [44] Only one series reported the live birth rate; this was 65% after 12 treatment cycles. [44] The RCT identified by the systematic review, which compared pulsatile GnRH after pretreatment with a GnRH agonist versus clomifene, may have been too small to detect a clinically important difference between treatments. [41]

Clinical guide:
Pulsatile GnRH is used in women with anovulation caused by low serum gonadotrophins and oestrogen concentrations (hypogonadotropic hypogonadism). Hypogonadotropic hypogonadism is a well defined condition and so evidence from case series should be generalisable to most affected women.

OPTION IN VITRO FERTILISATION IN OVULATION DISORDERS

Pregnancy and live birth rates
Immediate compared with delayed in vitro fertilisation Immediate in vitro fertilisation increases pregnancy and live birth rates in women with infertility from any cause at the end of treatment compared with delayed in vitro fertilisation (high-quality evidence).

Compared with intracytoplasmic sperm injection In vitro fertilisation is as effective as intracytoplasmic sperm injection at increasing pregnancy rates in women with various causes of infertility (moderate-quality evidence).

Note
We found no direct information about whether in vitro fertilisation is better than no active treatment in women with ovulation disorders.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

In vitro fertilisation versus no treatment:
We found no systematic review or RCTs comparing in vitro fertilisation (IVF) versus no treatment in women with ovulation disorders. However, RCTs are unlikely to be conducted.

Immediate versus delayed in vitro fertilisation:
See benefits of IVF under treatments for tubal infertility, p 17 .

In vitro fertilisation versus intracytoplasmic sperm injection:
See benefits of IVF under treatments for tubal infertility, p 17 .

Harms:

We found no RCTs (see harms of IVF under treatments for tubal infertility, p 17).

Comment:

One prospective cohort study compared 26 anovulatory women receiving IVF treatment (49 cycles assessed) versus 26 normo-ovulatory women with tubal infertility receiving IVF (46 cycles assessed). [45] It found no significant difference between anovulatory women and normo-ovulatory women in live birth, clinical pregnancy rates per cycle, miscarriage or multiple pregnancy rates after IVF

treatment (live birth: 8/49 [16%] in anovulatory women *v* 7/46 [15%] in normo-ovulatory women; P = 0.90; pregnancy rate: 16/49 [33%] *v* 12/46 [26%]; P = 0.5; miscarriage: 6/16 [38%] in anovulatory women *v* 2/12 [17%] in normo-ovulatory women; P = 0.2; multiple pregnancy (twins): 5/10 [50%] *v* 3/10 [30%]; P = 0.40. [45] The cohort study found no significant difference between women with polycystic ovary syndrome and normo-ovulatory women in cancellation of IVF treatment owing to hyper-response (2/49 [4%] cycles in women with PCOS *v* 2/46 [4%] cycles in normo-ovulatory women; reported as not significant; P value not reported).

Clinical guide:
These results suggest that IVF is as successful in anovulatory women as in normo-ovulatory women. It is unlikely that pregnancy rates between women with ovulation disorders and normo-ovulatory women will differ as anovulation does not affect uterine receptivity for implantation. Once ovulation is achieved, the chance of pregnancy should not differ.

OPTION INTRAUTERINE INSEMINATION PLUS CONTROLLED OVARIAN STIMULATION

We found no clinically important results about the effects of intrauterine insemination plus controlled ovarian stimulation treatment in women with ovulation disorders. Consensus regards this combination as likely to be beneficial for the treatment of women with unexplained infertility, or infertility owing to cervical hostility.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment:

Clinical guide:
It is interesting that there is a lack of evidence on the effects of intrauterine insemination plus controlled ovarian stimulation in the treatment of infertility caused by ovulation disorders. Consensus considers intrauterine insemination plus controlled ovarian stimulation as effective in the management of infertility owing to cervical hostility, unexplained infertility, and mild male factor infertility.

OPTION GONADOTROPHIN PRIMING OF OOCYTES BEFORE IN VITRO MATURATION

Pregnancy rates
Compared with no priming We don't know whether gonadotrophin priming (with recombinant follicle-stimulating hormone [follitropin], human chorionic gonadotrophin, or follitropin plus human chorionic gonadotrophin) of immature oocytes before in vitro maturation increases pregnancy rates compared with no priming in women with ovulation disorders (very low-quality evidence) in women with ovulation disorders.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Follicle stimulating hormone (follitropin) for priming:
We found one RCT (28 women with polycystic ovary syndrome (PCOS) who had not responded to greater-than or equal to 3 previous in vitro fertilisation treatments) which compared priming with follitropin (150 IU for 3 days, initiated on day 3 after menstruation, 24 cycles) before harvesting of immature oocytes versus no priming (12 cycles). [46] It found that priming with follitropin significantly increased pregnancy rates compared with no priming (0/12 [0%] with no priming *v* 7/24 [29%] with follitropin; P < 0.05). Pregnancy resulted in a live birth in 3/24 (12%) of women who received follitropin (P value not reported). [46]

Human chorionic gonadotrophin for priming:
We found one RCT (17 women with PCOS, 24 treatment cycles assessed) which compared priming with human chorionic gonadotrophin (hCG; 10 000 IU; 13 cycles) versus no priming (11 cycles). It found a similar clinical pregnancy rate in women who had priming with hCG compared with women who had no priming (5/13 [38%] with priming *v* 3/11 [27%] with no priming; significance not reported). [47]

Follicle stimulating hormone (follitropin) plus human chorionic gonadotrophin for priming:
We found one RCT (60 women with PCOS, 68 cycles assessed) comparing priming with follitropin (75 IU for 6 days; 35 cycles) plus hCG (10 000 IU, 36 hours before oocyte retrieval) versus priming with hCG alone (33 cycles). [48] It found no significant difference in pregnancy rates between priming with follitropin plus hCG and priming with hCG alone (31% with follitropin plus hCG *v* 36% with hCG alone; P = 0.799).

Harms: None of the RCTs gave any information on adverse effects. [46] [47] [48]

Comment: **Clinical guide:**
There is little information about the maturational capacity of immature oocytes derived from women with ovulation disorders who have been primed with gonadotrophins. In vitro maturation of oocytes may reduce the risk of ovarian hyperstimulation and may simplify treatment of women with ovulation disorders. However, the maturation rate of immature oocytes retrieved from women with ovulation disorders, particularly PCOS, is lower than that of those retrieved from women with normal menstrual cycles. [49] More RCTs are needed to reach a firm conclusion.

QUESTION What are the effects of treatments for tubal infertility?

OPTION SELECTIVE SALPINGOGRAPHY PLUS TUBAL CATHETERISATION

Pregnancy rates
Compared with hysteroscopy Selective salpingography plus tubal catheterisation is less effective than hysteroscopy at increasing pregnancy rates in women with tubal occlusion (moderate-quality evidence).

Note
We found no clinically important results about the effects of selective salpingography plus tubal catheterisation compared with no active treatment in women with tubal infertility.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits: We found no systematic review or RCTs.

Harms: Observational studies found that ectopic pregnancy occurred in 3–9% of women having selective salpingography and tubal catheterisation and that tubal perforation, which does not seem to be clinically important, occurred in 2%. [50] [51]

Comment: One systematic review (search date not reported) combined data from 10 cohort and other observational studies of selective salpingography and tubal cannulation (482 women), and four observational studies of hysteroscopic cannulation for proximal tubal blockage (133 women). [50] It found that hysteroscopy was associated with a higher pregnancy rate compared with selective salpingography and tubal catheterisation (pregnancies exceeding 20 weeks' gestation: 65/133 [49%] with hysteroscopy *v* 103/482 [21%] with salpingography). None of the observational studies included an untreated group, so it is not possible to estimate the treatment related pregnancy rate over and above the spontaneous pregnancy rate. Tubal patency and pregnancy without treatment have been reported in women diagnosed with bilateral proximal tube obstruction. [52]

OPTION TUBAL FLUSHING WITH OIL SOLUBLE MEDIA

Birth rate
Compared with no intervention Tubal flushing with oil-soluble media increases pregnancy rates comapred with no treatment in women with various causes of infertility (moderate-quality evidence).

Compared with water-based media Tubal flushing with oil-based media increases live birth rates compared with tubal flushing with water-based media in women with infertility from various causes (moderate-quality evidence).

Pregnancy rates
Compared with no intervention Tubal flushing with oil-soluble media increases pregnancy rates comapred with no treatment in women with various causes of infertility (moderate-quality evidence).

Compared with water-based media Tubal flushing with oil-based media does not increase pregnancy rates compared with tubal flushing with water-based media in women with infertility from various causes or because of tubal infertility (moderate-quality evidence).

Note
We found no clinically important results about tubal flushing solely in women with tubal infertility.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits: We found no systematic review or RCTs solely in women with tubal infertility (see comment below).

Oil soluble media versus no intervention:
We found one systematic review (search date 2001), which compared tubal flushing with oil soluble media versus no intervention in women with various causes of infertility. [53] It found that tubal flushing with oil soluble media significantly increased pregnancy rate and live birth compared with

no intervention (pregnancy: 3 RCTs; 58/195 [30%] with oil soluble media *v* 21/187 [11%] with no intervention; OR 3.30, 95% CI 2.00 to 5.43; live birth: 1 RCT; 23/73 [32%] with oil soluble media *v* 11/85 [13%] with no intervention; OR 2.98, 95% CI 1.40 to 6.37).

Oil soluble versus water soluble media:
We found one systematic review (search date 2001), which compared tubal flushing with oil soluble versus water soluble media. [53] The review found no significant difference in pregnancy rates between oil soluble media and water soluble media (6 RCTs; 1483 women; RR 1.16, 95% CI 0.98 to 1.38). [53] However, oil soluble media significantly increased live birth rates compared with water soluble media (2 RCTs; 931 women; RR 1.35, 95% CI 1.04 to 1.74). A subgroup analysis of women with tubal infertility found that oil soluble media did not significantly increase pregnancy rate compared with water soluble media (1 RCT; 2/12 [17%] with oil soluble media *v* 3/19 [16%] with water soluble media; RR 1.06, 95% CI 0.21 to 5.42). [53]

Harms:

Oil soluble media versus no intervention:
The systematic review found no significant difference between treatments in miscarriage per pregnancy (1 RCT; 4/28 [14%] with oil soluble medium *v* 2/14 [14%] with no intervention; RR 1.00, 95% CI, 0.21 to 4.81). [53]

Oil soluble versus water soluble media:
The systematic review found no significant difference between treatments in miscarriage or ectopic pregnancy (miscarriage per pregnancy; 1 RCT; 158 women: RR 0.86, 95% CI 0.52 to 1.43; ectopic pregnancy; 2 RCTs; 562 women: RR 0.48, 95% CI 0.09 to 2.58). The systematic review also found that oil soluble media reduced procedural pain and procedural complications (intravasation, infection, and haemorrhage) compared with water soluble media (pain: 2 RCTs; 54/206 [26%] with oil soluble media *v* 281/628 [45%] with water soluble media; RR 0.59, 95% CI 0.47 to 0.73; complications: 3 RCTs; 118/724 [16%] *v* 369/1368 [27%]; RR 0.67, 95% CI 0.57 to 0.80). [53]

Comment:

RCTs comparing oil soluble versus water soluble media were statistically heterogeneous. [53] One RCT included in the review only included women with unexplained infertility or mild endometriosis. [54]

Clinical guide:
The RCTs were not solely in women with tubal infertility and so may also be relevant to women with unexplained infertility.

OPTION TUBAL FLUSHING WITH WATER SOLUBLE MEDIA

Birth rate
Compared with oil-based media Tubal flushing with water-based media is less effective at increasing live birth rates compared with tubal flushing with oil-based media in women with infertility from various causes (moderate-quality evidence).

Pregnancy rates
Compared with oil-based media Tubal flushing with water-based media does not increase pregnancy rates compared with tubal flushing with oil-based media in women with infertility from various causes or because of tubal infertility (moderate-quality evidence).

Note
We found no clinically important results about tubal flushing solely in women with tubal infertility. We found no direct information about whether tubal flushing with water-based media is better than no active treatment.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

We found no systematic review or RCTs solely in women with tubal infertility (see comment below).

Water soluble media versus no intervention:
We found one systematic review (search date 2001), which found no RCTs comparing tubal flushing with water soluble media versus no intervention. [53]

Oil soluble versus water soluble media:
See benefits of tubal flushing with oil soluble media.

Harms:

Water soluble media versus no intervention:
We found no RCTs.

Oil soluble versus water soluble media:
See harms of tubal flushing with oil soluble media.

Comment: RCTs comparing oil soluble versus water soluble media were statistically heterogeneous. [53] One RCT included in the review only included women with unexplained infertility or mild endometriosis. [54]

Clinical guide:
The RCTs were not solely in women with tubal infertility and so may also be relevant to women with unexplained infertility.

OPTION TUBAL SURGERY

Birth rate
Compared with no treatment or medical treatment Tubal surgery increases live birth rates compared with no treatment or medical treatment in women with hydrosalpinges who are undergoing in vitro fertilisation (moderate-quality evidence).

CO_2 laser adhesiolysis compared wtih diathermy adhesiolysis CO_2 laser adhesiolysis is as effective as diathermy adhesiolysis at increasing live birth rates (moderate-quality evidence).

Pregnancy rate
Compared with no treatment or medical treatment Tubal surgery may increase pregnancy rates compared with no treatment or medical treatment in women with hydrosalpinges who are undergoing in vitro fertilisation (low-quality evidence).

CO_2 laser adhesiolysis compared wtih diathermy adhesiolysis CO_2 laser adhesiolysis is as effective as diathermy adhesiolysis at increasing pregnancy rates (moderate-quality evidence).

Adding postoperative treatments to tubal surgery compared with tubal surgery alone Tubal surgery plus additional treatments to prevent adhesion formation (steroids, dextran, noxytioline, postoperative hydrotubation, or second look laparoscopy) may be no more effective at increasing pregnancy rates compared with tubal surgery alone (low-quality evidence).

Note
We found no clinically important results about the effects of tubal surgery compared with in vitro fertilisation in women with tubal infertility.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Tubal surgery versus no treatment or medical treatment:
We found one systematic review (search date 2000, 3 RCTs, 295 women with hydrosalpinges having in vitro fertilisation [IVF] treatment; see comment below). [55] The review found that tubal surgery significantly increased pregnancy and live birth rates compared with no treatment or medical treatment (pregnancy rate: OR 1.75, 95% CI 1.07 to 2.86; live birth rate: OR 2.13, 95% CI 1.24 to 3.65; see comment below). [55]

Different types of tubal surgery versus each other:
We found one systematic review (search date not reported, 8 RCTs, 557 women, see comment below). [56] Two RCTs (130 women) identified by the review found no significant difference in pregnancy rates between CO_2 laser adhesiolysis and diathermy adhesiolysis (1 RCT; 16/30 [53%] with laser *v* 17/33 [52%] with diathermy; RR 1.04, 95% CI 0.65 to 1.67). One RCT identified by the review found no difference in pregnancy rates between CO_2 laser salpingostomy and diathermy salpingostomy (26/75 [35%] with laser *v* 16/60 [27%] with diathermy; RR 1.30, 95% CI 0.77 to 2.19). [56]

Adding postoperative treatments to tubal surgery:
We found two systematic reviews. [57] [58] The first review (search date not reported, 10 RCTs, 1086 women) compared tubal surgery plus additional treatments to prevent adhesion formation (steroids, dextran, and noxytioline) versus tubal surgery alone. [57] It found no significant difference in pregnancy rates between tubal surgery plus steroids (systemic or intraperitoneal) and no steroids (4 RCTs; OR 1.10, 95% CI 0.74 to 1.64), tubal surgery plus dextran (intraperitoneal) and no dextran (3 RCTs; OR 0.65, 95% CI 0.37 to 1.14), or tubal surgery plus noxytioline (intraperitoneal) and no noxytioline (1 RCT; OR 0.67, 95% CI 0.30 to 1.47). The second review (search date not reported, 5 RCTs, 588 women) compared early postoperative hydrotubation or second look laparoscopy plus adhesiolysis after tubal surgery versus control (late postoperative hydrotubation, postoperative irrigation with antibiotics plus late postoperative hydrotubation, no postoperative hydrotubation, or no second look laparoscopy). [58] It found that all the RCTs were either poor quality or underpowered.

It found insufficient evidence to support the routine practice of hydrotubation (1 RCT; OR 1.12, 95% CI 0.57 to 2.21) or second look laparoscopy (2 RCTs; OR 0.96, 95% CI 0.44 to 2.07) after tubal surgery.

Tubal surgery versus in vitro fertilisation:
We found no RCTs (see comment below).

Harms:

Tubal surgery versus no treatment or medical treatment:
The review found no significant difference between tubal surgery and no treatment or medical treatment in the rate of ectopic pregnancy, miscarriage per pregnancy, or treatment related complications (ectopic pregnancy: OR 0.42, 95% CI 0.08 to 2.14; miscarriage: OR 0.49, 95% CI 0.16 to 1.52; complications: OR 5.80, 95% CI 0.35 to 96.79). [55] Tubal surgery involves general anaesthesia and admission to hospital. There is a risk of ectopic pregnancy caused by pre-existing tubal damage; retrospective studies have reported rates of 7–9% with tubal surgery, compared with 1–3% with IVF. [59] [60] IVF carries the risk of multiple pregnancy and ovarian hyperstimulation syndrome (see harms of IVF under treatments for tubal infertility, p 17).

Adding postoperative treatments to tubal surgery:
One systematic review found no significant difference between hydrotubation after tubal surgery and no postoperative hydrotubation in ectopic pregnancy or miscarriage rates (ectopic pregnancy: 1 RCT; 9/129 [7%] with hydrotubation *v* 4/86 [5%] with no hydrotubation; RR 1.61, 95% CI 0.51 to 5.07; miscarriage: 1 RCT; 8/17 [47%] *v* 3/13 [23%]; RR 2.04, 95% CI 0.67 to 6.21). [58]

Tubal surgery versus IVF:
We found no RCTs.

Comment:

Tubal surgery versus no treatment or medical treatment:
In the systematic review comparing tubal surgery versus non-surgical treatment, although a variety of different surgical techniques were used, laparoscopic unilateral or bilateral salpingectomy were the most common (numerical data not reported). [55]

Different types of tubal surgery versus each other:
Of the eight RCTs included in the review, five RCTs were small, used outdated surgical techniques, and had problems relating to methods of randomisation, and therefore did not meet *BMJ Clinical Evidence* inclusion criteria. [56] These data precede recent improvements in case selection and laparoscopic training. One additional systematic review (search date not reported, 7 observational studies, 279 women with proximal tubal blockage) compared microsurgery (275 women) versus macrosurgery (104 women). [50] It found that microsurgery significantly increased pregnancy rates compared with macrosurgery (RR 2.2, 95% CI 1.5 to 3.2).

Clinical guide:
Success rates with tubal surgery depend on the severity and site of disease. The best figures from surgery in women with distal tubal occlusion are live birth rates of 20–30%, with rates of 40–60% reported for the less common proximal occlusion. [61] [62] [63] [64] [65]

Tubal surgery versus in vitro fertilisation:
Fertility rates from case series of tubal surgery and from large databases of couples having IVF suggest that tubal surgery is as effective as IVF in women with filmy adhesions, mild distal tubal occlusion, or proximal obstruction. [61] [66] [67] [68] [69] [70] If successful, tubal surgery allows women to have more pregnancies without further medical intervention and without the risks associated with IVF. [71]

OPTION IN VITRO FERTILISATION IN TUBAL OBSTRUCTION

Pregnancy and live birth rates
Immediate compared with delayed in vitro fertilisation Immediate in vitro fertilisation increases pregnancy and live birth rates in women with infertility from any cause at the end of treatment compared with delayed in vitro fertilisation (high-quality evidence).

Compared with intracytoplasmic sperm injection In vitro fertilisation is as effective as intracytoplasmic sperm injection at increasing pregnancy rates in women with various causes of infertility including tubal infertility (moderate-quality evidence).

Note
We found no clinically important results about the effects of in vitro fertilisation compared with no treatment or with tubal surgery in women with tubal infertility alone.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

In vitro fertilisation versus no treatment:
We found no RCTs.

Immediate versus delayed in vitro fertilisation:
We found one RCT (399 couples with any cause of infertility; the couples who received delayed in vitro fertilisation (IVF) acted as untreated controls for at least 6 months), which found that immediate IVF significantly increased pregnancy rate and number of live births compared with delayed IVF (pregnancy rate: 33/190 [17%] with immediate IVF *v* 13/163 [8%] with delayed IVF; RR 2.43, 95% CI 1.18 to 5.07; number of live births: 22/190 [12%] with immediate IVF *v* 8/163 [5%] with delayed IVF; RR 2.36, 95% CI 1.03 to 5.66). [72]

In vitro fertilisation versus tubal surgery:
We found no RCTs. See comment of tubal surgery, p 16 .

In vitro fertilisation versus intracytoplasmic sperm injection:
We found one systematic review (search date 2002, 1 RCT) which compared IVF (224 cycles assessed) versus intracytoplasmic sperm injection (ICSI; 211 cycles assessed) in women with various causes of infertility including tubal infertility. [73] The RCT found no significant difference in pregnancy rates between treatments (72/219 [33%] with IVF *v* 53/204 [26%] with ICSI; RR 1.27, 95% CI 0.95 to 1.72). [74]

Harms:

In vitro fertilisation versus no treatment:
We found no RCTs.

Immediate versus delayed in vitro fertilisation:
The RCT found no difference between treatments in the overall rate of miscarriage or ectopic pregnancy however, the study may have been too small to detect a clinically important difference (miscarriage: 6/33 [18%] with immediate IVF *v* 2/13 [15%] with delayed IVF; significance not reported; ectopic pregnancy: 5/33 [15%] *v* 3/13 [23%]; significance not reported). [72]

In vitro fertilisation versus tubal surgery:
We found no RCTs. See comment of tubal surgery, p 16 .

In vitro fertilisation versus intracytoplasmic sperm injection:
The RCT identified by the review found no significant difference between treatments in multiple pregnancy rate (17/72 [24%] with IVF *v* 16/53 [30%] with intracytoplasmic sperm injection [ICSI]; RR 0.78, 95% CI 0.43 to 1.40). [73] [74] It also found that ovarian hyperstimulation syndrome occurred in seven (4%) IVF cycles and nine (5%) ICSI cycles (significance not reported). [74]

Comment:

Clinical guide:
The success of IVF is influenced by a woman's age, duration of infertility, and previous pregnancy history. [8] Pregnancy rates are highest between the ages of 25 years and 35 years and decline steeply after 35 years. Similar clinics, which describe the same methods, report different success rates for IVF. [8] In the UK Human Fertilisation and Embryology Authority database, the average live birth rate per IVF cycle over 2000–2001 was 22% if ICSI cycles were taken into account. [75] The equivalent average figure in the USA is 25%, but again results vary among centres. [76] [77] In the UK, larger centres (greater-than or equal to 200 cycles a year) report slightly higher live birth rates than smaller centres (20% per cycle started compared with 16%). [78] Such a difference has not been reported consistently in the USA.

Multiple births:
Of the 6309 live births after IVF in the UK in 2000–2001, 27% were multiple, including 109 (2%) triplets. [75] In the UK, the number of embryos that can be replaced is restricted to two. [75] In the USA, where there are no such restrictions, 15 367 live births included 38% multiple births, 6% of which were triplets and above. [76]

Ovarian hyperstimulation syndrome:
One non-systematic review suggested that severe ovarian hyperstimulation syndrome occurs in 0.5–2.0% of all IVF cycles. [79]

Obstetric outcome:
We found one systematic review (search date 1998, 42 high quality observational studies) that compared obstetric outcome in mothers receiving IVF versus either a population based control group or a selected control group matched for different variables. [80] It found that children born after IVF had a considerably higher risk of being born preterm and with a lower birth weight than

children conceived naturally, although this was likely to be because of the high incidence of multiple births and maternal characteristics such as nulliparity, increased age, previous infertility, and obstetric history (absolute numbers not reported). There was no evidence of an increased overall incidence of congenital malformations in children born after conventional IVF or after embryo cryopreservation.

QUESTION What are the effects of treatments for infertility associated with endometriosis?

OPTION DRUG-INDUCED OVARIAN SUPPRESSION

Pregnancy rate
Compared with placebo Ovulation-suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives, and gonadotrophin-releasing hormone analogues) do not increase pregnancy rates compared with placebo in women with endometriosis (moderate-quality evidence).

Compared with danazol Ovulation suppression does not increase pregnancy rates compared with danazol in women with endometriosis (moderate-quality evidence).

Compared with laparoscopic ablation of endometrial deposits Medical ovulation suppression may be less effective at increasing pregnancy rates compared with laparoscopic ablation of endometrial deposits (very low-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Drug-induced ovarian suppression versus placebo:
We found one systematic review (search date not reported, 7 RCTs, 402 women with visually diagnosed endometriosis who had been attempting conception for < 12 months), which compared ovulation suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives, and gonadotrophin releasing hormone analogues) versus placebo. [81] It found no significant difference in pregnancy rates between ovulation suppression agents and placebo (62/207 [30%] with suppression agents *v* 69/195 [35%] with placebo; OR 0.74, 95% CI 0.48 to 1.15). [81]

Drug-induced ovarian suppression versus danazol:
We found one systematic review (search date not reported, 10 RCTs, 843 women with visually diagnosed endometriosis who had been attempting conception for < 12 months). [81] It found no significant difference in pregnancy rates between ovulation suppression agents and danazol (187/514 [36%] with suppression agents *v* 102/329 [31%] with danazol; OR 1.30, 95% CI 0.97 to 1.76). [67]

Drug-induced ovarian suppression versus surgery:
See benefits of laparoscopic ablation of endometrial deposits, p 20 .

Harms:

Drug-induced ovarian suppression versus placebo:
The review found that ovulation suppression agents caused adverse effects that included weight gain, hot flushes, and osteoporosis (data not reported). [81]

Drug-induced ovarian suppression versus danazol:
The review found that the adverse effects of danazol were dose related and included an average weight gain of 2–4 kg with 3 months' treatment; androgenic effects such as acne, seborrhoea, hirsutism, and voice changes; and general complaints, including irritability, musculoskeletal pains, and tiredness (data not reported). [81]

Drug-induced ovarian suppression versus surgery:
See harms of laparoscopic ablation of endometrial deposits, p 20 .

Comment:

In the review, three of the RCTs used a combination of clomifene (clomiphene) plus ovarian suppression agents. [81] The results reported in the review suggest that while ovulation suppression is useful for the management of endometriosis related pain, the use of ovulation suppression has no significant effect on endometriosis related infertility.

OPTION INTRAUTERINE INSEMINATION PLUS GONADOTROPHINS

Live birth rate
Compared with no treatment Intrauterine insemination plus gonadotrophins (follicle-stimulating hormone) increases live birth rates compared with no treatment in women with minimal or mild endometriosis (high-quality evidence).

Pregnancy rate

Compared with intrauterine insemination alone Intrauterine insemination plus gonadotrophins (follicle-stimulating hormone) increases live birth rates after the first treatment cycle compared with intraueterine insemination alone in women with endometriosis (high-quality evidence).

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Intrauterine insemination plus gonadotrophins versus no treatment or expectant management:
We found one RCT. [82] The RCT (103 couples with infertility associated with minimal or mild endometriosis) compared intrauterine insemination (IUI) plus gonadotrophins (follicle stimulating hormone [FSH] 53 couples, 127 cycles) versus no treatment (50 couples, 184 cycles). [82] It found that IUI plus FSH significantly increased live birth rate per cycle compared with no treatment (14/127 [11%] with IUI plus FSH *v* 4/184 [2%] with no treatment; OR 5.6, 95% CI 1.8 to 17.4). [82]

Intrauterine insemination plus gonadotrophins versus intrauterine insemination alone:
We found one RCT (119 couples with primary pelvic or cervical factor infertility for a mean of 3.7 years, 57 couples with infertility associated with endometriosis), which compared alternate cycles of gonadotrophins (human menopausal gondadotrophin [hMG]) plus IUI versus IUI alone. [83] It found that hMG plus IUI significantly increased the pregnancy rate after the first treatment cycle compared with IUI alone (11/58 [19%] with hMG plus IUI *v* 0/61 [0%] with IUI alone; P = 0.0002). Subgroup analysis of the 57 couples with endometriosis, found that hMG plus IUI significantly increased the pregnancy rate per cycle compared with IUI alone (15/127 [12%] with hMG plus IUI *v* 2/96 [2%] with IUI alone; RR 5.1, 95% CI 1.1 to 22.5). [83]

Harms:

Intrauterine insemination plus gonadotrophins versus no treatment or expectant management:
No cases of severe ovarian hyperstimulation were reported in the RCT. [82] The RCT also reported two twin births and one triplet birth with IUI plus FSH.

Intrauterine insemination plus gonadotrophins versus intrauterine insemination alone:
The RCT reported a miscarriage rate of 24.2% and a multiple birth rate of 18.2% with gonadotrophin (hMG) plus IUI (data for IUI treatment alone not reported). No cases of severe ovarian hyperstimulation requiring hospital admission were reported in the RCT. [83]

Comment:

We found one systematic review (search date 2002, 3 RCTs, 386 women), which compared single versus double inseminations in stimulated cycles of IUI. [84] The RCT found no significant difference between single and double IUI in the pregnancy rate per couple (OR 1.45, 95% CI 0.78 to 2.68). One small crossover RCT assessed the timing of insemination in clomifene (clomiphene) stimulated cycles. [85] It found similar pregnancy rates per cycle whether insemination was timed with a urinary luteinising hormone kit or whether ultrasound monitoring with human chorionic gonadotrophin induction of ovulation was used.

OPTION LAPAROSCOPIC ABLATION

Pregnancy rate
Compared with medical or no treatment Laparoscopic ablation of endometrial deposits may increase pregnancy rates compared with medical treatment or no treatment (very low-quality evidence).

Compared with diagnostic laparoscopy Laparoscopic ablation or resection of endometrial deposits increases live birth rates and ongoing pregnancy rates compared with diagnostic laparoscopy (high-quality evidence).

Note
We found no clinically important results about the effects of laparoscopic surgery compared with no treatment or compared with ovarian suppression.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

Laparoscopic ablation versus no treatment or ovarian suppression:
We found no RCTs (see comment below).

Laparoscopic surgery versus diagnostic laparoscopy:
We found one systematic review (search date 2000–2001, 2 RCTs, 437 women), which compared laparoscopic surgery (ablation or resection of endometrial deposits) versus diagnostic laparoscopy. [86] It found that laparoscopic surgery significantly increased the proportion of women who had a live birth or pregnancy continuing beyond 20 weeks compared with diagnostic laparoscopy (60/223 [27%] with laparoscopic surgery *v* 39/214 [18%] with diagnostic laparoscopy; RR 1.48, 95% CI 1.03 to 2.11). See also laparoscopic ablation of endometrial deposits under endometriosis.

Harms:

Laparoscopic ablation versus no treatment or ovarian suppression:
We found no RCTs.

Laparoscopic surgery versus diagnostic laparoscopy:
The review found no significant difference between laparoscopic surgery and diagnostic laparoscopy in the proportion of women who miscarried or who had operative complications (miscarriage: 15/223 [6.7%] with laparoscopic surgery *v* 11/214 [5.1%] with diagnostic laparoscopy; RR 1.31, 95% CI 0.62 to 2.78; operative complications: 3/172 [1.7%] *v* 1/169 [0.6%]; RR 2.95, 95% CI 0.31 to 28.06). [86] One multicentre series of 29 966 diagnostic and operative gynaecological laparoscopies found a mortality of 3.3/100 000 laparoscopies and a complication rate of 3.2/1000 laparoscopies. [87]

Comment:

In the larger RCT comparing laparoscopic surgery versus diagnostic laparoscopy, 48/341 (14%) women who received laparoscopic surgery for their endometriosis also had periadnexal adhesions treated, which may have affected their fertility. [86] We found one systematic review (search date not reported) [88] and one non-systematic review, [89] which together identified 21 cohort studies and one quasi-randomised trial in a total of 3879 women with all stages of endometriosis. Interventions were laparoscopic or open surgery versus medical treatment or no treatment. The non-systematic review combined data from all 21 studies and found that surgery significantly increased pregnancy rates compared with medical treatment or no treatment (RR 1.4, 95% CI 1.3 to 1.5). [89] It found no significant difference in pregnancy rates between laparoscopic and open surgery (RR 0.9, 95% CI 0.8 to 1.0). It found that, in women with mild or minimal endometriosis, laparoscopic surgery significantly increased pregnancy rates compared with danazol or no treatment (OR 2.7, 95% CI 2.1 to 3.5; absolute results presented graphically).

Clinical guide:
The risks and morbidity of surgery under general anaesthesia and of postoperative adhesion formation need to be balanced against the adverse effects of treatments involving ovarian suppression or stimulation.

OPTION IN VITRO FERTILISATION IN ENDOMETRIOSIS

Pregnancy and live birth rates
Immediate compared with delayed in vitro fertilisation Immediate in vitro fertilisation increases pregnancy and live birth rates in women with infertility from any cause at the end of treatment compared with delayed in vitro fertilisation (high-quality evidence).

Compared with intracytoplasmic sperm injection In vitro fertilisation is as effective as intracytoplasmic sperm injection at increasing pregnancy rates in women with various causes of infertility including tubal infertility (moderate-quality evidence).

Note
We found no direct information about whether in vitro fertilisation is better than no active treatment in women with infertility associated with endometriosis.

For GRADE evaluation of interventions for female infertility, see table, p 26 .

Benefits:

In vitro fertilisation versus no treatment:
We found no systematic review or RCTs which compared in vitro fertilisation (IVF) versus no treatment in women with endometriosis related infertility (see comment below).

Immediate versus delayed in vitro fertilisation:
See benefits of IVF under treatments for tubal infertility, p 17 .

In vitro fertilisation versus intracytoplasmic sperm injection:
See benefits of IVF under treatments for tubal infertility, p 17 .

Harms:

See harms of in vitro fertilisation under treatments for tubal infertility, p 17 .

Comment:

We found one systematic review [90] and two retrospective cohort studies [91] [92] that examined the effects of endometriosis compared with other causes of infertility, or the effects of severity of endometriosis, on IVF outcome. The cohort studies found no significant difference in pregnancy rates between groups. [91] [92] The systematic review (search date 1999, 22 non-randomised studies) found that women with endometriosis were less likely to become pregnant than women with infertility because of blocked or damaged tubes (pregnancy assessed by human chorionic gonadotrophin levels; adjusted OR 0.56, 95% CI 0.44 to 0.70). [90] There is a need for properly controlled prospective randomised studies that present fertility rates with IVF in different stages of

endometriosis using a validated classification system. Comparisons with assisted reproductive techniques are also required.

Clinical guide:
In the UK Human Fertilisation and Embryology Authority database, the average live birth rate per IVF cycle over 2000–2001 was 22% if intracytoplasmic sperm injection cycles were taken into account. [75]

GLOSSARY

Adhesiolysis Division of adhesions, which are bands of scar tissue that form after infection or surgery.
Anovulation is the failure to ovulate (expel a mature oocyte) owing to dysfunction of the ovary or suppression by drug treatment. Anovulation is a common cause of female infertility. Most often, women who do not ovulate also do not menstruate (amenorrhea).
Delayed in vitro fertilisation In vitro fertilisation treatment after 6 months of being assessed in an infertility clinic after at least 12 months of infertility.
Endometriosis is a progressive disease which occurs when the endometrial tissue lining the uterus grows outside the uterus and attaches to the ovaries, fallopian tubes or other organs in the abdominal cavity. Symptoms include painful menstrual periods, abnormal menstrual bleeding, and pain during or after sexual intercourse.
Gonadotrophin priming of oocytes This is the in vitro maturation of oocytes using gonadotrophins (hormones stimulate and control reproductive activity) from the germinal vesicle (early) stage of development to the metaphase II (mature) stage.
Hydrosalpinges is the abnormal distension of one or both fallopian tubes owing to fluid build up, usually because of inflammation.
Hydrotubation Flushing of the fallopian tubes through the cervix and uterine cavity to remove surgical debris and reduce the incidence of tubal reocclusion.
Immediate in vitro fertilisation In vitro fertilisation treatment within 6 months of being assessed in an infertility clinic after at least 12 months of infertility.
In vitro fertilisation (IVF) is a technique where female oocytes (eggs) are fertilised with sperm from a male partner outside the body in a fluid medium in the laboratory. Embryos are transferred later to the uterus using a special catheter.
Laparoscopic ovarian drilling (ovarian diathermy) Ovarian drilling can be performed laparoscopically by either cautery or laser vapourisation (using CO_2 , argon, or Nd:YAG lasers), which are used to create multiple perforations (about 10 holes per ovary) of the ovarian surface and stroma (inner area of the ovary). This is thought to cause ovulation by restoring the intra-ovarian hormonal environment to normal, which in turn beneficially affects the hypothalamic–pituitary–ovarian axis.
Macrosurgery Surgery without dedicated optical magnification.
Microsurgery Surgery involving optical magnification to allow the use of much finer instruments and suture material in addition to a non-touch technique, with the aim of minimising tissue handling and damage.
Ovarian hyperstimulation syndrome (OHSS) can occur in mild, moderate, and severe forms. Mild ovarian hyperstimulation syndrome is characterised by fluid accumulation, as shown by weight gain, abdominal distension, and discomfort. Moderate ovarian hyperstimulation syndrome is associated with nausea and vomiting, ovarian enlargement, abdominal distension, discomfort, and dyspnoea. Severe ovarian hyperstimulation syndrome is a life threatening condition, in which there is contraction of the intravascular volume, tense ascites, pleural and pericardial effusions, severe haemoconcentration, and the development of hepatorenal failure. Deaths have occurred, caused usually by cerebrovascular thrombosis, renal failure, or cardiac tamponade.
Ovulation disorders are defined by the failure of an ovum to be expelled owing to a malfunction in the ovary. Ovulation disorders are a major cause of infertility and can often be corrected with medication. Ovulation disorders often result in infrequent menstruation (oligomenorrhea).
Pituitary downregulation (long protocol) This is the process by which the release of gonadotrophins from the pituitary gland is stopped after repeated administration of gonadotrophin releasing hormone (GnRH) analogues, this in turn controls reproductive function.
Polycystic ovary syndrome (PCOS) results from an accumulation of incompletely developed follicles in the ovaries owing to chronic anovulation. PCOS is characterised by irregular or absent menstrual cycles, multiple small cysts on the ovaries (polycystic ovaries), mild hirsutism, and infertility. Many women also have increased insulin resistance.
Pulsatile gonadotrophin releasing hormone is a hormone produced and released by the hypothalamus at intervals (pulses). Pulsatile gonadotrophin releasing hormone controls the production and release of gonadotrophins from the pituitary gland, which in turn controls reproductive function.
Salpingography is a technique used to diagnose blockages in the fallopian tubes. It involves the radiographic imaging of the fallopian tubes after the injection of radio-opaque contrast medium (dye) through the cervix to the uterine cavity. If the fallopian tubes are open the dye flows into the tubes and then spills out to the abdominal cavity. This is documented in a series of x-ray images during the procedure. If tubes are blocked from the proximal end, a very narrow catheter is introduced under radiographic imaging (selective salpingography and tubal catheterisation) to remove the obstruction if possible.
Second look laparoscopy Laparoscopy performed some time after tubal surgery (either open or laparoscopic) with the aim of dividing adhesions relating to the initial procedure.

Tubal flushing involves injecting an oil or water soluble contrast medium into the fallopian tubes to flush out any blockages in the tubes. Flushing out any tubal "plugs" which may be causing proximal tubal occlusion using oil or water soluble media may have a fertility enhancing effect.
Tubal infertility is the inability to conceive owing to a blockage in one or both fallopian tubes and is a common cause of infertility. The tubal blockages are usually caused either by pelvic infection, such as pelvic inflammatory disease (PID) or endometriosis. Blockages may also be caused by scar tissue that forms after pelvic surgery.
Tubal surgery techniques are used to restore the patency of the fallopian tubes in women with tubal infertility as an alternative to in vitro fertilisation. Surgery may either be open microsurgery or laparoscopic microsurgery.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

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Female infertility

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Disclaimer

TABLE **GRADE evaluation of interventions for female infertility**

Important outcomes	Pregnancy rates, live birth rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for infertility caused by ovulation disorders?									
2 (192) [12]	Pregnancy rate	Clomifene *v* placebo	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect size point added for RR greater than 2
2 (152) [13] [14]	Pregnancy rate	Clomifene *v* tamoxifen	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (173) [16]	Pregnancy rate	Clomifene *v* clomifene plus metformin	4	0	0	–1	+1	High	Directness point deducted for narrow inclusion criteria. Effect size point added for OR greater than 2
1 (28) [[41]	Pregnancy rate	Clomifene *v* pulsatile gonadotrophin releasing hormone plus GnRH agonist	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria
5 (at least 33,537) [20] [93] [22] [23] [21]	Ovarian cancer	Clomifene *v* no clomifene	2	0	–1	0	0	Very low	Consistency point deducted for conflicting results
2 (50) [16]	Live birth rate	Metformin *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria
5 (172) [16]]	Pregnancy rate	Metformin *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria
1 (161) [38]	Pregnancy rates	Metformin *v* ovarian drilling	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for narrow inclusion criteria
1 (213) [24]	Pregnancy rate	Cyclofenil *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for broad inclusion criteria
4 (396) [[25]	Pregnancy rate	Human menopausal gonadotrophin *v* urinary follicle-stimulating hormone	4	0	0	–2	0	Low	Directness points deducted for narrow inclusion criteria and interventions
4 (1214) [26]	Pregnancy or live births	Human menopausal gonadotrophins *v* recombinant follicle-stimulating hormone	4	0	0	–2	0	Low	Directness point deducted for narrow inclusion criteria and interventions
3 (457) [27]	Pregnancy rates	Recombinant follicle-stimulating hormone *v* urinary follicle stimulating hormone	4	0	0	–2	0	Low	Directness point deducted for narrow inclusion criteria and interventions
6 (371) [35] [36] [37]	Pregnancy rate	Gonadotrophins *v* laparoscopic ovarian drilling	4	0	0	–1	0	Moderate	Directness point deducted for narrow inclusion criteria
1 (200) [23]	Ovarian cancer	Human menopausal gonadotrophins *v* control	2	–1	0	0	+1	Low	Quality point deducted for methodological flaws. Effect size point added for RR greater than 2
10 RCTs [[29]	Pregnancy rate	Gonadotrophin-releasing hormone agonists plus gonadotrophins *v* gonadotrophins alone	4	0	0	–1	0	Moderate	Directness point deducted for broad inclusion criteria

Important outcomes	Pregnancy rates, live birth rates, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
6 (552) [30]	Pregnancy rate	Depot gonadotrophin-releasing hormone agonist *v* daily gonadotrophin-releasing hormone agonist	4	0	0	0	0	High	
26 RCTs [31]	Pregnancy rates	Long *v* short gonadotrophin-releasing hormone agonist protocol	4	0	0	0	0	High	
9 (1014) [32]	Pregnancy rate	Intranasal gonadotrophin-releasing hormone agonists *v* other routes	4	0	0	–1	0	Moderate	Directness point deducted for uncertain clinical relevance of outcome measure
5 (1796) [34]	Pregnancy rates	Gonadotrophin-releasing hormone antagonist *v* gonadotrophin-releasing hormone agonists	4	0	0	–1	0	Moderate	Directness point deducted for broad inclusion criteria
1 (399) [[72]	Pregnancy /live birth rate	Immediate *v* delayed in vitro fertilisation	4	0	0	–1	+1	High	Directness point deducted for different duration of treatment between groups. Effect size point added for RR greater than 2
1 (423) [73]	Pregnancy rate	In vitro fertilisation *v* intracytoplasmic sperm injection	4	0	0	–1	0	Moderate	Directness point deducted for broad inclusion criteria
3 (105) [46] [47] [48]	Pregnancy rates	Priming with gonadotrophins *v* no priming	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
What are the effects of treatments for tubal infertility?									
10 (615) [50]	Pregnancy rate	Selective salpingography plus tubal catheterisation *v* hysteroscopy	2	0	0	0	+1	Moderate	Effect size point added for RR greater than 2
3 (382) [53]	Pregnancy rate	Tubal flushing with oil-soluble media *v* no treatment	4	–1	0	–1	+1	Moderate	Quality point deducted for statistical heterogeneity. Directness point deducted for broad inclusion criteria. Effect size point added for OR greater than 2
1 (158) [53]	Birth rate	Tubal flushing with oil soluble media *v* no treatment	4	–1	0	–1	+1	Moderate	Quality point deducted for sparse data. Directness point deducted for broad inclusion criteria. Effect size point added for OR greater than 2
6 (1483) [53]	Pregnancy rate	Tubal flushing with oil-based media *v* water-based	4	0	0	–1	0	Moderate	Directness point deducted for broad inclusion criteria
2 (931) [53]]	Live birth rate	Tubal flushing with oil-based media *v* water-based	4	0	0	–1	0	Moderate	Directness point deducted for broad inclusion criteria
3 (295) [55]	Pregnancy rate	Tubal surgery *v* no treatment/medical treatment	4	0	0	-2	0	Low	Directness points deducted for narrow inclusion criteria and use of different comparators
3 (295) [55]	Live birth rate	Tubal surgery *v* no treatment/medical treatment	4	0	0	–2	+1	Low	Directness points deducted for narrow inclusion criteria and use of different comparators. Effect size point added for RR greater than 2
1 (63) [56]	Pregnancy rate	CO_2 laser adhesiolysis *v* diathermy adhesiolysis	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	Pregnancy rates, live birth rates, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (63) [56]	Birth rate	CO_2 laser adhesiolysis v diathermy adhesiolysis	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
10 (1674) [58] [57]	Pregnancy rate	Postoperative treatments plus surgery *v* tubal surgery alone	4	–1	0	–1	0	Low	Quality points deducted for methodological flaws. Directness point deducted for wide range of interventions
What are the effects of treatments for infertility associated with endometriosis?									
7 (402) [81]	Pregnancy rate	Ovulation suppression *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for wide range of interventions
10 (843) [81]	Pregnancy rate	Ovulation suppression *v* danazol	4	0	0	–1	0	Moderate	Directness point deducted for wide range of interventions
21 (3879) [89]	Pregnancy rate	Medical ovulation suppression *v* laparoscopic ablation of endometrial deposits	2	–1	0	–1	0	Very low	Quality point deducted for incomplete reporting of results. Directness point deducted for wide range of interventions
1 (103 couples) [82]	Birth rate	Intrauterine insemination plus gonadotrophins *v* no treatment	4	–1	0	–1	+2	High	Quality point deducted for sparse data. Directness point deducted for narrow inclusion criteria. Effect size points added for OR greater than 5
1 1 (57 couples) [83]	Pregnancy rate	Intrauterine insemination plus gonadotrophins *v* intrauterine insemination alone	4	–1	0	0	+2	High	Quality point deducted for sparse data. Effect size points added for OR greater than 5
2 (437) [86]	Live birth or pregnancy rate	Laparoscopic surgery *v* diagnostic laparoscopy	4	0	0	0	0	High	

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.